REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1, 20, 24-25, 28-31 and 33-34 are pending in the above-referenced patent application and are currently under examination. With entry of this Amendment, claim 1 has been amended. More particularly, in order to expedite prosecution, claim 1 has been amended to recited "wherein the immune cells of said human are reduced or eliminated prior to transplantation." Moreover, in order to expedite prosecution, the "thereby" clause of claim 1 has been amended to remove the term "preventing" and to recite that "HIV entry into the immune cell of said human is facilitated by the CCR5 receptor." No new matter is introduced with the amendments to claim 1. Reconsideration is respectfully requested.

In the Office Action, claims 1, 15-17, 20, 24-25, 27-31 and 33-34 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly being indefinite. In addition, claims 1, 15-17, 20, 24-25, 27-31, and 33-34 remain provisionally rejected under the under the judicially created doctrine of obviousness type double patenting as allegedly being unpatentable over claims 1, 20, 24-25, 28-31 and 33-34 of co-pending U.S. Patent Application No. 10/498,450. For convenience, the Examiner's rejections are addressed in the order presented in the Office Action.

II. Rejection Under 35 U.S.C. §112, First Paragraph, Enablement

Claims 1, 15-17, 20, 24-25, 27-31, and 33-34 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly indefinite. In support of this rejection, the Examiner alleges, in essence, that in order to practice the claimed invention, one of skill would allegedly be required to perform "undue experimentation." To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

It is well established that a specification is presumed to be in compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph. The burden is therefore on the Patent Office to establish a reasonable basis to question enablement. The test for enablement is whether one reasonably skilled in the art could make and use the claimed invention from the

disclosure in the specification coupled with information known in the art without undue experimentation. For the reasons set forth below, Applicants respectfully submit that one reasonably skilled in the art could make and used the claimed invention ***without*** undue experimentation.

Claim 1, as amended, is directed to a method of treating HIV infection in a human, wherein HIV entry into an immune cell is facilitated by a CCR5 receptor. In this method, the human is transplanted with a stem cell-rich population of cells from a human donor, *i.e.*, umbilical cord blood. The stem cell-rich population of cells has a beneficial gene that is a homozygous polymorphism in a CCR5 gene and the encoded CCR5 receptor is unable to facilitate HIV entry into the immune cell. The CCR5 receptor polymorphism is selected from a 32 basepair deletion in the coding region of the CCR5 gene or a CCR5m303 mutant.

Applicants respectfully submit that the amendment to claim 1 renders moot the Examiner's concern that the claims are not directed to treating an HIV infection that requires CCR5 for entry into the immune cell of the human being treated. As amended, both the preamble and the body of claim 1 make it clear that the presently claimed method is directed to treating HIV invention, wherein HIV entry into the immune cell of the human is facilitated by a CCR5 receptor. As pointed out by John Zaia, M.D. in his Declaration filed pursuant to 37 C.F.R. §1.132:

> ***Most HIV strains use the CCR5 co-receptor for entry into and infection of a host immune cell.*** Cells that do not express a functional CCR5 co-receptor are less susceptible to infection by HIV strains, even those HIV strains that do not use the CCR5 co-receptor for cellular entry. Other receptors are available for infection with HIV, and therefore CCR5-/- persons can be infected. ***However, CCR5 is the most important of all such co-receptors and remains the most important receptor for natural HIV infection.***"

(*See*, paragraph 7 of the Declaration of Dr. John Zaia, which was filed in the USPTO on July 9, 2008 (hereinafter, the "Zaia Declaration") (emphasis added)). Moreover, as pointed out by Dr. Zaia infection by CXCR4 virus is rare and the CCR5 co-receptor plays an important role in

promoting HIV entry and infection. In support of this position, Dr. Zaia cites the Arenzana-Seisdedos *et al.* reference, a reference previously cited by the Examiner, which states:

> The strong protection of homozygotes was confirmed in subsequent studies, . . . but a few seropositive individuals were reported as homozygous for Δ32, demonstrating that protection is incomplete. In some of these cases, the HIV strain was characterized as using exclusively CXCR4 as co-receptor. **These *rare cases of initial transmission and propagation of X4 viruses further underline the preponderant role of played by CCR5 and R5 viruses in the initiation of HIV infection and the paradox of the inefficient transmission or evolution of X4 viruses despite the constitutive expression of CXCR4 in CD-4-expressing cells and the abundance of these HIV target cells.***

(*See*, paragraph 7 of the Zaia Declaration, citing Arenzana-Seisdedos *et al.*, *Sem. Immunol.* 18:387-403 (2006) (emphasis added, citations deleted)). Thus, it is Dr. Zaia's opinion that "transplantation of a CCR5 -/- immune system will likely benefit a majority of patients infected with the HIV-1 virus by reducing the ability of the HIV-1 virus to enter cells of the transplanted patient" (Id.).

In fact, this has proven to be more than true. As pointed out by Dr. Zaia, the specification discloses transplantation of CCR5 homozygous mutations to treat HIV infection (*see*, paragraph 11 of the Zaia Declaration). Moreover, as pointed by Dr. Zaia, a recent report from Hütter *et al.*, which was attached to the Zaia Declaration as Exhibit H, confirms the therapeutic benefit of transplantation of CCR5 homozygous mutations to treat HIV infection. Specifically, Hütter *et al.* observed in a single case report of a matched unrelated CCR5 -/- adult donor of allogeneic blood progenitor cells, used for transplantation into an HIV/AIDS patient with leukemia, that there was a resultant beneficial outcome in which the recipient became HIV negative by RT-PCR assay and was off antiretroviral therapy at one-year post transplant. Importantly, it is Dr. Zaia's opinion that "cord blood transplantation of homozygous CCR5 mutant cells to treat HIV infection will provide results similar to those reported by Hütter *et al.* for bone marrow transplantation to treat HIV infection" (*see*, paragraph 11 of the Zaia Declaration).

In the Office Action, the Examiner alleges that "applicants' arguments and declaration is not commensurate with the scope of the claims particularly since claimed method differ significantly from method disclosed by Hutter on several counts" (*see*, pages 5-6 of the Office Action). The Examiner alleges that "method disclosed by Hutter uses CD34+ enriched population that is different from starting cell for transplantation claimed in the instant method" (*see*, page 5 of the Office Action). However, as pointed out by Dr. Zaia in his Declaration: "[u]mbilical cord blood transplants are typically performed using uncultured umbilical cord blood cells and modification is not required to practice the claimed method. Thousands of cord blood transplants have been performed and the methodology is standardized" (*see*, page 9 of the Zaia Declaration). Moreover, as pointed out by Dr. Zaia: "[i]t is my experience that transplantation of umbilical cord cells does not require identification or isolation of a particular subset of hematopoietic stem cells to provide a therapeutic benefit" (*see*, paragraph 15 of Dr. Zaia's Declaration). Thus, even though there is a difference in starting materials between the presently claimed method and the Hütter *et al.* method, it is Dr. Zaia's opinion that "cord blood transplantation of homozygous CCR5 mutant cells to treat HIV infection will provide results similar to those reported by Hütter *et al.* for bone marrow transplantation to treat HIV infection" (*see*, paragraph 11 of the Zaia Declaration).

In addition, the Examiner alleges that "Hutter discloses using cells from HLA-identical donors and transplanting cells in patient conditioned with FLAMSA regimen. . . ., which would deplete marrow blast, while none of the instantly claimed method requires these steps" (*see*, page 6 of the Office Action). The specification makes it clear that "[t]ypically, the normal stem cell population (which ultimately produces the lymphocytes susceptible to viral replication) is eliminated or reduced prior to transplantation of the therapeutic stem cell units. Chemotherapy, radiation or the techniques described in U.S. Pat. No. 6,217,867 are used to condition the bone marrow for appropriate engraftment of the transplant" (*see*, *e.g.*, page 12, lines 14-19 of the specification). Moreover, as pointed out by Dr. Zaia in his Declaration, "[t]housands of cord blood transplants have been performed and the methodology is standardized" (*see*, page 9 of the Zaia Declaration). Clearly, based on the teachings of the specification, it was clear to those of skill in the art that the cells of the person's own immune

system are eliminated or reduced by, *e.g.*, chemotherapy or total body irradiation prior to prior to transplantation of umbilical cord blood. This step was standard operating procedure (SOP) at the time of the present invention, However, in order to expedite prosecution, claim 1 has been amended to recite that the "the immune cells of said human are reduced or eliminated prior to transplantation." Thus, claim 1, as amended, now recites the step that the Examiner felt was missing from the claim.

Further, the Examiner alleges that "Hutter discloses measuring HIV viremia by RNA and proviral DNA in peripheral blood and bone marrow cells just prior to discontinuing highly active anti retroviral therapy (HAART)" and that "the specification does not provide any guidance with respect to measuring HIV viremia, proviral DNA or any other assay (RT, western) to show that method as claimed could reduce HIV infection. . . ." (*see*, page 6 of the Office Action). Applicants respectfully submit that, at the time of the invention, one reasonably skilled in the art could readily measure HIV viremia ***without*** undue experimentation. To say otherwise is incorrect and severely underestimates the level of skill in the art at the time of the present invention.

In view of the foregoing remarks and the previously filed Zaia Declaration, Applicants respectfully submit that claim 1, as amended, as well as dependent claims 20, 24, 25, 28-31, 33 and 34 are fully enabled by the specification as originally filed. As attested to by Dr. Zaia in his Declaration, "the specification discloses transplantation of CCR5 homozygous mutations to treat HIV infection, " and the "transplantation of a CCR5 -/- immune system will likely benefit a majority of patients infected with the HIV-1 virus by reducing the ability of the HIV-1 virus to enter cells of the transplanted patient" (*see*, paragraphs 11 and 7, respectively, of the Zaia Declaration). Moreover, Applicants respectfully submit that the scope of enablement provided by the specification bears more that a "reasonable correlation" to the scope of the claims (*see*, MPEP 2164.08). Accordingly, Applicants urge the Examiner to withdraw this enablement rejection under 35 U.S.C. § 112, first paragraph.

III. Obviousness-Type Double Patenting Rejection

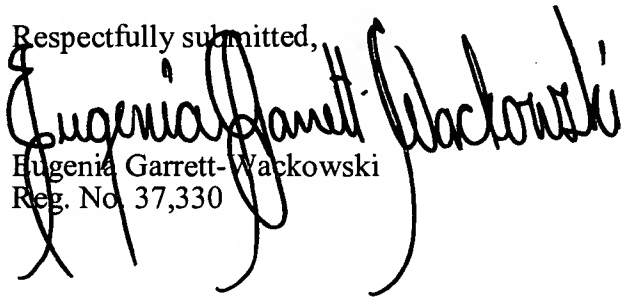
Claims 1, 15-17, 20, 24-25, 27-31, and 33-34 remain provisionally rejected under the judicially created doctrine of obviousness type double patenting as allegedly being unpatentable over claims 1, 20, 24-25, 28-31 and 33-34 of co-pending U.S. Patent Application No. 10/498,450. As previously noted, Applicants will file a Terminal Disclaimer to overcome this obviousness-type double patenting rejections, if appropriate, when the present claims are deemed otherwise allowable.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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Attachments
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